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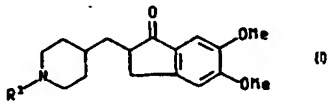
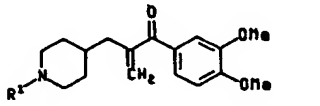
(54) Title: PROCESSES AND INTERMEDIATES FOR PREPARING 1-BENZYL-4-((5,6-DIMETHOXY-1-INDANON)-2-YL)METHYLPIPERIDINE

(57) Abstract

The present invention relates to a process for preparing a compound of formula (I), wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is (C_1-C_4)alkyl, and R^3 is (C_1-C_4)alkyl or phenyl optionally substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo or trifluoromethyl, comprising: a) reacting a compound of formula (III), wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is (C_1-C_4)alkyl, and R^3 is (C_1-C_4)alkyl or phenyl optionally substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo or trifluoromethyl, with a methenylation agent to form a compound of formula (II), wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is (C_1-C_4)alkyl, and R^3 is (C_1-C_4)alkyl or phenyl optionally substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo or trifluoromethyl and; b) reacting said compound of formula (II), so formed, with a strong acid. The present invention further comprises the additional step of reacting the compound of formula (I) with hydroxide to form a compound of formula (VI), and reacting said compound of formula (VI) so formed with a benzyl halide and a base to form a compound of formula (VII). The present invention relates also to the novel intermediates of formulae (I), (II) and (III).



(I)



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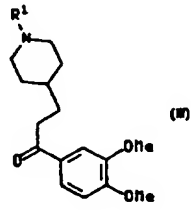

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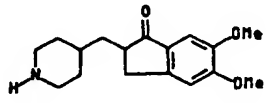

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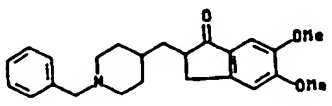

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PROCESSES AND INTERMEDIATES FOR PREPARING 1-BENZYL-4-((5,6-DIMETHOXY-1-INDANON)-2-YL)METHYLPIPERIDINE

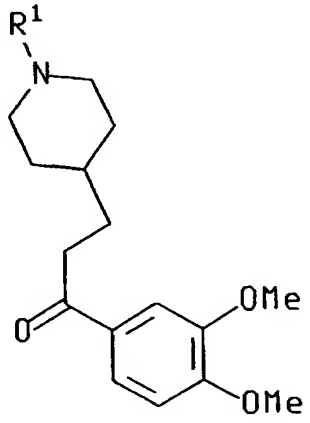
Background of the Invention

This invention relates to a novel process for the preparation of 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine (E2020), the compound of the formula VII below, and to novel intermediates used in said process.

United States Patent 4,895,841, issued January 23, 1990, refers to 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine, methods for its preparation, useful intermediates, and to methods and pharmaceutical compositions for treating diseases caused by acetylcholinesterase activity, such as senile dementia. United States Patent 4,895,841, issued January 23, 1990, is hereby incorporated by reference in its entirety.

Summary of the Invention

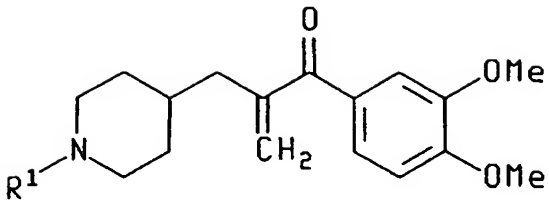
The present invention relates to a compound of the formula



III

wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is $(C_1$-$C_4)$alkyl, and R^3 is $(C_1$-$C_4)$alkyl or phenyl optionally substituted with from one to three substituents independently selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo or trifluoromethyl.

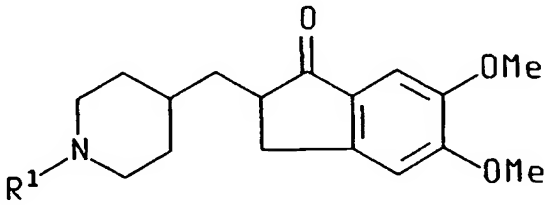
The present invention also relates to a compound of the formula



II

wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is (C_1-C_4)alkyl, and R^3 is (C_1-C_4)alkyl or phenyl optionally substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo or trifluoromethyl.

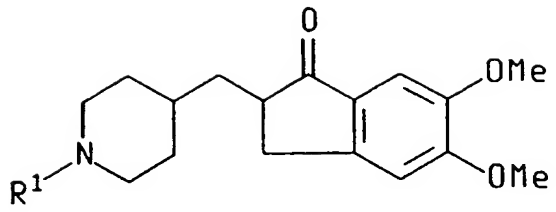
The present invention also relates to a compound of the formula



I

wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is (C_1-C_4)alkyl, and R^3 is (C_1-C_4)alkyl or phenyl optionally substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo or trifluoromethyl.

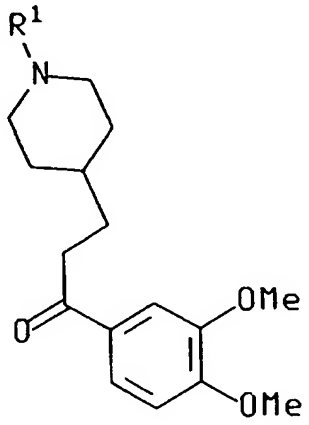
The present invention also relates to a process for preparing a compound of the formula



I

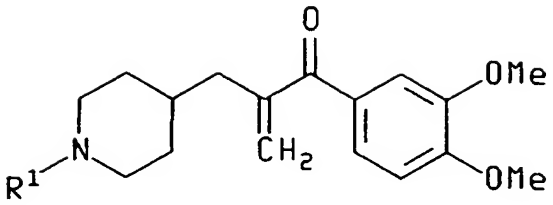
wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is (C_1-C_4)alkyl, and R^3 is (C_1-C_4)alkyl or phenyl optionally substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo or trifluoromethyl, comprising:

a) reacting a compound of the formula



III

wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is (C_1-C_4)alkyl, and R^3 is (C_1-C_4)alkyl or phenyl optionally substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo or trifluoromethyl, with a methenylation agent to form a compound of the formula



II

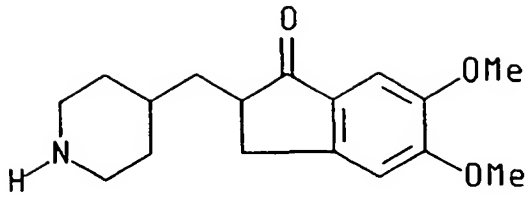
wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is (C_1-C_4)alkyl, and R^3 is (C_1-C_4)alkyl or phenyl optionally substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo or trifluoromethyl and;

b) reacting said compound of formula II, so formed, with a strong acid.

Preferably, said methenylation agent is tetramethyldiaminomethane in acetic anhydride. More preferably, said tetramethyldiaminomethane and acetic anhydride are added in excess. Most preferably, said tetramethyldiaminomethane comprises 2 molar equivalents (relative to the amount of the compound of the formula III) and said acetic anhydride comprises 4 molar equivalents (relative to the amount of the compound of the formula III).

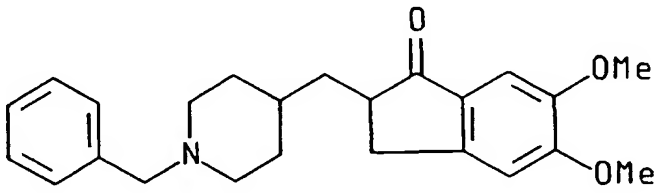
Preferably, said strong acid is sulfuric acid. More preferably, said sulfuric acid is concentrated sulfuric acid. Most preferably, said concentrated sulfuric acid comprises 9 molar equivalents (relative to the amount of said compound of the formula II).

A preferred embodiment of the present invention relates to any of the above processes further comprising the additional step of reacting the compound of formula I, wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is (C_1-C_4)alkyl, and R^3 is (C_1-C_4)alkyl or phenyl optionally substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo or trifluoromethyl, with hydroxide (preferably potassium hydroxide) to form a compound of the formula



VI

and reacting said compound of formula VI so formed with a benzyl halide and a base to form a compound of the formula

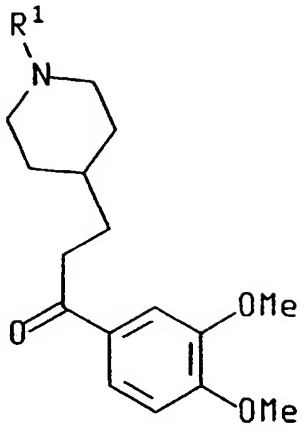


VII

Preferably, said benzyl halide is benzyl bromide. Preferably said base is triethanolamine.

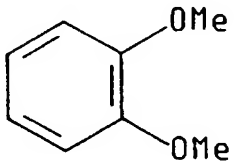
The most preferred embodiment of the above invention relates to a process wherein said compound of formula I is isolated before it is converted to the compound of formula VI. The compound of formula I can be isolated by addition of the strongly acidic solution containing the compound of formula I to ice/water followed by extraction with an organic solvent and removal of the organic solvent.

The present invention also related to a process for preparing a compound of the formula



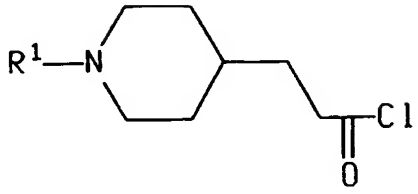
III

comprising reacting a compound of the formula



IV

with a compound of the formula



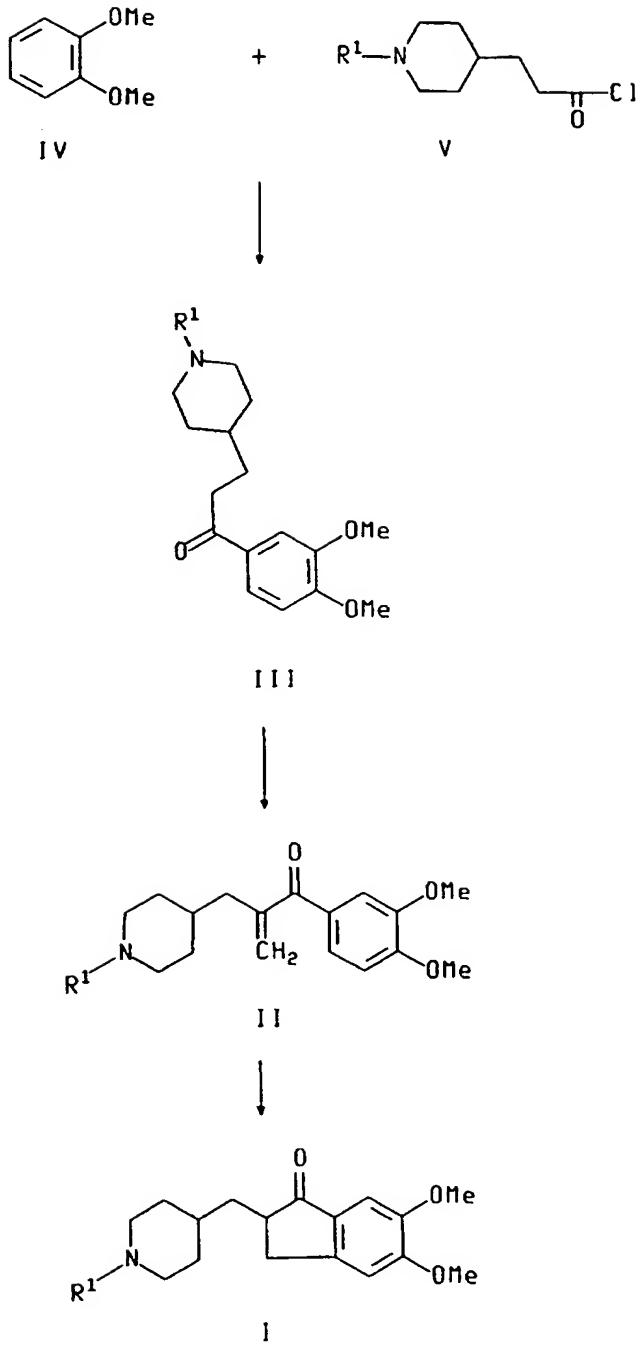
V

in the presence of a Lewis acid, such as aluminum trichloride, in a reaction inert solvent, such as methylene chloride.

Detailed Description of the Invention

The compounds of formula I and E2020 can be prepared as described in the following reaction schemes and discussion. Unless otherwise indicated, compounds of the formulae I, II and III, VI and VII and the groups R^1, R^2 and R^3 in the reaction schemes and discussion that follow are as defined above.

SCHEME 1


OMe
OMe
+
R1
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Cl
O
IV
V
R1
N
O
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III
O
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II
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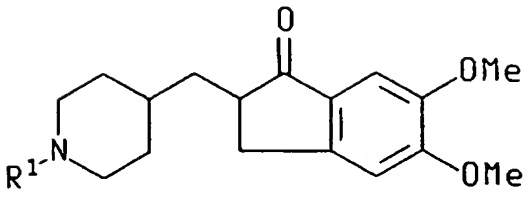
SCHEME 2



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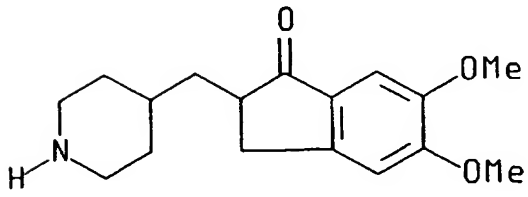
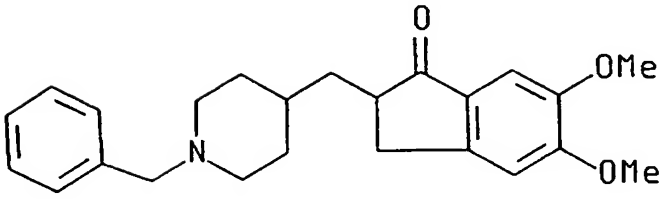


VI



VII

Scheme 1 refers to the process of preparing a compound of formula I, which can be converted to a compound of the formula VII, E2020, by the methods of Scheme 2.

Referring to Scheme 1, the compound of the formula IV is commercially available. Compounds of the formula V are also commercially available or can be prepared by methods well known to those of ordinary skill in the art. United States Patent Application 08/329,352, filed October 26, 1994, also refers to the preparation of compounds of the formula V.

A compound of the formula III can be prepared from a compound of the formula IV by reacting said compound of the formula IV with a compound of the formula V, wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is $(C_1$-$C_4)$alkyl, and R^3 is $(C_1$-$C_4)$alkyl or phenyl optionally substituted with from one to three substituents independently selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo or trifluoromethyl, in the presence of a Lewis acid in a reaction inert solvent. Preferably, R^1 is $R^2O(C=O)$-, and R^2 is methyl. Suitable Lewis acids include aluminum trichloride, titanium tetrachloride or boron trichloride, preferably aluminum trichloride. Suitable reaction inert solvents include methylene chloride or dichloroethane, preferably methylene chloride. The reaction is generally performed at a temperature from about 0°C to about 85°C, preferably about 30°C.

A compound of the formula II can be prepared from a compound of the formula III by reacting said compound of the formula III with a methenylation agent. Preferably, R^1 is $R^2O(C=O)$-, and R^2 is methyl. Suitable methenylation agents include tetramethyldiaminomethane in acetic anhydride, formaldehyde (about 37 weight % in water) in diethylamine, formaldehyde (about 37 weight % in water) in piperidine or N-methylthiomethylpiperdine. Preferably the methenylation agent is tetramethyldiaminomethane in acetic anhydride. When tetramethyldiaminomethane in acetic anhydride is the methenylation agent it is preferable to perform the reaction with an excess of tetramethyldiaminomethane and acetic anhydride. Most preferably, the reaction is performed with 4 equivalents of acetic anhydride (relative to the amount of the compound of formula III) and 2 equivalents of tetramethyldiaminomethane (relative to the amount of the compound of formula III). When the methenylation agent is other than tetramethyldiaminomethane in acetic anhydride a solvent may be used to facilitate the reaction. Suitable solvents include acetic anhydride, ethers (e.g., diethyl ether and tetrahydrofuran), methanol, acetic acid or dioxane, preferably acetic anhydride. The

reaction is performed at a temperature from about 0°C to about 90°C, preferably at about 90°C. The reaction time may vary from about 6 hours to about 30 hours. Preferably the reaction time is about 12 hours.

A compound of the formula I can be prepared from a compound of the formula II by reacting said compound of the formula II with a strong acid in a reaction inert solvent. Suitable strong acids include concentrated sulfuric acid, aluminum trichloride or concentrated hydrochloric acid, preferably concentrated sulfuric acid. When aluminum trichloride is the acid, a solvent must be used. Suitable solvents include carbon disulfide, methylene chloride or dichloroethane, preferably carbon disulfide. The reaction is performed at a temperature from about 0°C to about 100°C, preferably at about 25°C.

Scheme 2 refers to the conversion of compounds of the formula I into E2020, the compound of the formula VII.

Referring to Scheme 2, a compound of the formula I can be converted into a compound of the formula VI by reaction with a strong base in the presence of a solvent. Preferably, the reactant is a compound of the formula I, wherein R^1 is $R^2O(C=O)$-, and R^2 is methyl. Suitable bases include potassium hydroxide and sodium hydroxide, preferably potassium hydroxide. Suitable solvents include lower alcohols, water or mixtures thereof, preferably a 2:1 water/methanol mixture. The reaction is performed at a temperature from about 25°C to about 100°C preferably at about 100°C. The reaction time may vary from about 6 to about 24 hours, preferably about 18 hours.

The compound of formula I is most preferably converted into a compound of formula VI by isolating the compound of formula I before converting it into the compound of formula VI. A compound of formula I is isolated by pouring the acidic solution containing the compound of formula I over an ice/water mixture and extracting the aqueous with an organic solvent. Suitable solvents include methylene chloride, ethyl acetate or dichlorothane, preferably methylene chloride. The organic layer can be concentrated and is then suitable for treatment with a strong base.

A compound of the formula VII can be prepared from a compound of the formula VI by reacting said compound of the formula VI with a benzyl halide in a reaction inert solvent. Suitable halides include chloride, bromide, and iodide, preferably bromide. Suitable reaction inert solvents include diethyl ether, isopropyl ether,

tetrahydrofuran, preferably isopropyl ether. The reaction is performed at a temperature from about 0°C to about 70°C, preferably about 70°C.

The compound of formula VII can be converted to pharmaceutically acceptable acid addition salts of the compound of the formula VII. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the compound of formula VII are those which form non-toxic acid addition salts, e.g., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [e.g., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

The compound of the formula VII is basic in nature and is therefore capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula VII from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

Compounds of the formula VII, E2020, and its pharmaceutically acceptable salts can be used to treat a disease caused by acetylcholinesterase activity, such as Alzheimers' Disease, according to the methods described in United States Patent 4,895,841, issued January 23, 1990.

Specifically, United States Patent 4,895,841 states that the *in vitro* acetyl cholinesterase activity of 1-benzyl-4-((5,6-diethyoxy-1-indanon)-2yl)methyl piperidine, E2020, or a pharmaceutically acceptable salt thereof can be determined according to the method of Ellman et al. Biochem. Pharmacol., 7, 88-95 (1961).

The acetylcholinesterase inhibitory activity of 1-benzyl-4-((5,6-diethyoxy-1-indanon)-2yl)methyl piperidine, determined according to the method of Ellman et al., expressed in terms of 50% inhibitory concentration (IC_{50}) is 0.0053 μM.

Other methods for determining the activity of 1-benzyl-4-((5,6-diethyoxy-1-indanon)-2yl)methyl piperidine are described in United States Patent 4,895,841, issued January 23, 1990.

1-Benzyl-4-((5,6-dimethoxy-1-indanon)-2yl)methylpiperidine is effective for treatment, prevention, remission, improvement, etc. of various kinds of senile dementia, particularly senile dementia of the Alzheimer's type; cerebrovascular disease accompanying cerebral apoplexy, e.g. cerebral hemorrhage or cerebral infarcts, cerebral arteriosclerosis, head injury, etc.; and aprosexia, disturbance of speech, hypobulia, emotional changes, recent memory disturbance, hallucinatory-paranoid syndrome, behavioral changes, etc. accompanying encephalitis, cerebral palsy, etc.

Further, 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2yl)methylpiperidine has a strong and highly selective anticholinesterase action, which also renders the compound useful as a pharmaceutical based on this mode of action.

Specifically, 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2yl)methyl-piperidine is effective for, for example, Huntington's chorea, Pick's disease and delayed ataxia or tardive dyskinesia other than senile dementia of the Alzheimer type.

When 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2yl)methylpiperidine is used as a pharmaceutical for these diseases, it may be orally or parenterally administered. In general, it is parenterally administered in the form of injections, such as intravenous, subcutaneous, and intramuscular injections, suppositories, or sublingual tablets. The dose will vary depending upon the symptom; age, sex, weight, and sensitivity of patients; method of administration; time and intervals of administration and properties, dispensing, and kind of pharmaceutical preparations so that there is no particular limitation with respect to the dose. Normally the compound may be administered in a dose of about 0.1 to 300 mg, preferably 1 to 100 mg, per day per adult, ordinarily in one to four portions.

Pharmaceutical preparations in the dosage form of, e.g., injections, suppositories, sublingual tablets, tablets, and capsules are prepared according to methods which are commonly accepted in the art.

In preparing injections, the effective ingredient is blended, if necessary, with a pH modifier, a buffer, a suspending agent, a solubilizing agent, a stabilizer, a tonicity agent, a preservative, etc., followed by preparation of an intravenous, subcutaneous, or intramuscular injection according to an ordinary method. In this case, if necessary, it is possible to lyophilize these preparations according to an ordinary method.

Examples of the suspending agents include methylcellulose, Polysorbate 80®, hydroxyethylcellulose, acacis, powdered tragacanth, sodium carboxymethylcellulose, and polyoxyethylene sorbitan monolaurate.

Examples of the solubilizing agent include polyoxyethylene hydrogenated castor oil, Polysorbate 80®, nicotinamide, polyoxyethylene sorbitan monolaurate, Macrogol®, and an ethyl ester of castor oil fatty acid.

Examples of stabilizer include sodium sulfite, sodium metasulfite, and ether, and examples of the preservative include methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, sorbic acid, phenol, cresol, and chlorocresol.

The following Examples illustrate the preparation of the compounds of the present invention and the preparation of E2020. Commercial reagents were utilized without further purification. Melting points are uncorrected. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent and were obtained on a Bruker 300 MHz instrument. D_2O refers to deuterium oxide. $CDCl_3$ refers to deuterochloroform. Chromatography, unless otherwise noted, refers to column chromatography performed using 32-63μm silica gel and executed under nitrogen pressure (flash chromatography) conditions. Thin Layer Chromatograph (TLC) refers to chromatography performed on silica gel plates (E. Merck, Kiesel Gel 60 F254) and eluted with the specific solvent designated. High Pressure Liquid Chromatography (HPLC) was performed on a LDC Analytical constaMetric® 3200 HPLC (Thermo Separation Products Co.). A Zorbax®C8, 60Å, 3.9 x 150 mm column (Mac-Mod Analytical, Inc., Chadds Ford, PA 19317) was used for HPLC analysis and was eluted with the solvent indicated. Fast Atom Bombardment Mass Spectrometry (FABMS) refers to Mass Spectroscopic analysis on a Hewlett-Packard 5989 Mass Spectrometer (Particle beam chemical ionization). Room temperature refers to 20-25°C.

Preparation 1

3-Pyridin-4-ylpropen-2-oic acid

To a solution of pyridin-4-ylcarboxaldehyde (100 gm, 0.93 mol) in pyridine (100 mL) was added malonic acid (100 gm, 0.96 mol) at 90°C. After carbon dioxide (CO_2) evolution subsided, the reaction slurry was diluted with methanol. The title compound was isolated as a white solid by filtration (97 gm, 70% yield).

^{1}H NMR (HOAc-d_4) δ 11.70 (s, 1H), 8.85 (d, 2H), 7.95 (d, 2H), 7.80 (d, 1H), 6.90 (d, 1H).

Preparation 2

3-Piperidin-4-ylpropanoic acid

The product from Preparation 1 (32 gm, 0.22 mol) was dissolved in 2 N hydrochloric acid (150 mL) and treated with 10 weight percent of 5% rhodium on carbon under a hydrogen atmosphere (45 p.s.i.) until hydrogen gas uptake ceased. The catalyst was filtered and the resulting solution of the title compound was carried directly into the next step.

^{1}H NMR (D_2O) δ 3.25 (m, 2H), 2.80 (m, 2H), 2.25 (t, 2H), 1.75 (m, 2H), 1.50-1.10 (m, 5H). FABMS $(M + 1)^+ = 157$.

Preparation 3

3-[N-(Methoxycarbonyl)-piperidin-4-yl]proprionic acid

The solution of the product from Preparation 2, was brought to pH 12 with aqueous potassium hydroxide. To this solution was added methyl chloroformate (21 mL, 0.27 mol). After one hour, the solution was brought to pH 1 with 6 N hydrochloric acid and extracted with dichloromethane. The organic layer was dried with sodium sulfate and the dichloromethane displaced with isopropyl ether. The titie compound was isolated as a solid by filtration (39 gm, 84%).

Mp 89-90°C. ^{1}H NMR ($CDCl_3$) δ 4.10 (m, 2H), 3.65 (s, 3H), 2.70 (m, 2H), 2.35 (t, 2H), 1.80 -1.10 (m, 7H). FABMS $(M + 1)^+ = 216$.

Example 1

4-(2-Chlorocarbonyl-ethyl)-piperidine-1-carboxylic acid methyl ester

To a solution of the product from Preparation 3 (54.0 gm, 0.251 mol) in dichloromethane (500 mL) was added dimethylformamide (0.39 mL, 0.02 equivalents) and oxalyl chloride (22 mL, 0.26 mol). After gas evolution subsided, the formation of the title compound was complete. The solution of the title compound was carried

directly into the next step.

Example 2

4-[3-(3,4-Dimethoxy-phenyl)-3-oxo-propyl]-piperidine-1-carboxylic acid methyl ester

To the solution of the product from Example 1 at room temperature was added (25.5 mL, 0.20 mol) of 1,2-dimethoxybenzene followed by portion-wise addition of aluminum trichloride (100 gm, 0.75 mol). The reaction mixture was stirred for 4 hours at room temperature. High pressure liquid chromatography analysis showed that the reaction was complete. The reaction was quenched by careful addition of water and then extracted with methylene chloride (2x500 mL). The combined organic extracts were washed with 1 N sodium hydroxide (200 mL), followed by brine (200 mL). Finally, the organic layer was dried over sodium sulfate. The solution was filtered and the solvent was removed *in vacuo* to provide an oil (67 gm, quantitative crude weight). Thin Layer Chromatographic (TLC) and High Pressure Liquid Chromatographic (HPLC) analysis indicated that the product was of sufficient purity to proceed directly into the next step.

The progress and purity of these reactions was monitored by both TLC and High Pressure Liquid Chromatography using the systems indicated (R_f and t_r for reaction product):

TLC (silica gel): R_f= 0.50 (40 : 60 hexane/ethyl acetate). High Pressure Liquid Chromatography retention time (t_r) was 12.6 min (Zorbax C_8, 254 nm, 1 mL/min, 600:400:2:1 water/acetonitrile/triethylamine/acetic acid). ^{1}H NMR ($CDCl_3$) δ 7.55 (dd, 1H, J = 8.4, 2.0 Hz), 7.50 (d, 1H, J = 2.0 Hz), 6.86 (d, 1H, J = 8.4 Hz), 4.02-4.20 (m, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.65 (s, 3H), 2.93 (t, 2H, J = 7.3 Hz), 2.64-2.78 (m, 2H), 1.61-1.76 (m, 4H), 1.40-1.55 (m, 1H), 1.06-1.21 (m, 2H). FABMS $C_{18}H_{25}NO_5$ $(M + 1)^+$ = 336.

Example 3

4-[2-(3,4-Dimethoxy-benzoyl)-allyl]-piperidine-1-carboxylic acid methyl ester

To a solution of the product from Example 2 (66.0 gm, 0.20 mol) was added acetic anhydride (76.0 mL, 0.80 mol) followed by tetramethyldiaminomethane (54 mL, 0.40 mol). The reaction exothermed to 90°C. After the exotherm was complete, the reaction was heated at 90°C for three hours and then allowed to stir overnight at room

temperature.

An aliquot (1 ml) was removed from the reaction vessel and treated with cold hydrochloric acid. The solution was extracted with methylene chloride followed by treatment with aqueous bicarbonate. The organic layer was then dried and analyzed by High Pressure Liquid Chromatography which showed that the starting material was consumed.

Based on the purity of the crude reaction mixture, the crude reaction material was carried directly into the next step,

TLC (silica gel): R_f = 0.60 (40 : 60 hexane/ethyl acetate). High Pressure Liquid Chromatography retention time (t_r) was 15.9 min (Zorbax C_8, 254 nm, 1 mL/min, 600:400:2:1 water/acetonitrile/triethylamine/acetic acid). ^{1}H NMR ($CDCl_3$) δ 7.35-7.40 (m, 2H), 6.83 (d, 1H, J = 8.8 Hz), 5.68 (s, 1H), 5.54 (s, 1H), 3.94-4.14 (m, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.62 (s, 3H), 2.59-2.75 (m, 2H), 2.32-2.41 (m, 2H), 1.55-1.74 (m, 3H), 1.00-1.21 (m, 2H). FABMS $C_{19}H_{25}NO_5$ $(M + 1)^+$ = 348.

Example 4

4-(5,6-Dimethoxy-1-oxo-indan-2-ylmethyl)-piperidine-1-carboxylic acid methyl ester

The crude reaction mixture from Example 3, (0.20 mol) was treated with concentrated sulfuric acid (100 mL) at 0°C. The reaction was then allowed to stir overnight at room temperature, at which time High Pressure Liquid Chromatographic analysis indicated that the reaction was complete. The reaction was quenched by pouring onto 1 kg of ice, and the aqueous phase was then extracted with methylene chloride (2x500 mL). The combined organic extracts were washed with 500 mL of water, 500 mL of 1 N sodium hydroxide, 500 mL of brine, dried over sodium sulfate, and the volatiles removed *in vacuo*. The oily solid was then triturated with 500 mL of isopropyl ether, and the product was filtered to provide 46.5 gm (68% from dimethoxybenzene, 88% per step) of the title compound as a yellow solid.

TLC (silica gel) R_f = 0.40 (40 : 60 hexane/ethyl acetate). High Pressure Liquid Chromatography retention time (t_r) was 10.1 min (Zorbax C_8, 254 nm, 1 mL/min, 600:400:2:1 water/acetonitrile/triethylamine/acetic acid). ^{1}H NMR ($CDCl_3$) δ 7.15 (s, 1H), 6.85 (s, 1H), 4.08-4.23 (m, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 3.67 (s, 3H), 3.24 (dd, 1H, J = 17.8, 8.3 Hz), 2.62-2.82 (m, 4H), 1.84-1.95 (m, 1H), 1.62-1.80 (m, 3H), 1.25-1.39 (m, 1H), 1.08-1.33 (m, 2H). FABMS $C_{19}H_{25}NO_5$ $(M + 1)^+$ = 348.

Example 5

5,6-Dimethoxy-2-piperidin-4-ylmethyl-indan-1-one

To a solution of the product from Example 4 (5.0 gm, 14.4 mmol) in methanol (40 mL) was added potassium hydroxide (4.9 gm, 87 mmol) dissolved in 80 mL of water. The mixture was then heated under a nitrogen atmosphere overnight, at which time high pressure liquid chromatographic analysis indicated that the starting material was consumed. The aqueous phase was extracted with methylene chloride (3x50 mL), the combined organic layers dried with sodium sulfate, and the volatiles stripped *in vacuo* to provide 3.30 gm (79%) of the title compound as a solid. This material was used without further purification.

High Pressure Liquid Chromatography retention time (t_r) was 2.45 min (Zorbax C_8, 254 nm, 1 mL/min, 600:400:2:1 water/acetonitrile/triethylamine/acetic acid). ^1H NMR ($CDCl_3$) δ 7.12 (s, 1H), 6.82 (s, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.20 (dd, 1H, J = 17.7, 8.2 Hz), 3.00-3.13 (m, 2H), 2.52-2.77 (m, 4H), 1.70-1.94 (m, 1H), 1.51-1.80 (m, 3H), 1.02-1.35 (m, 3H). FABMS $C_{17}H_{23}NO_3$ $(M + 1)^+ = 290$.

Example 6

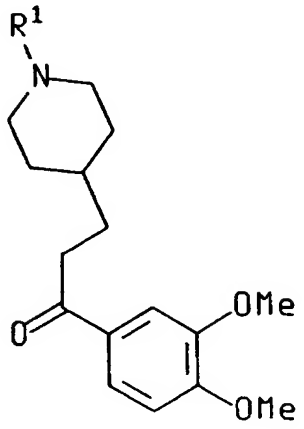
2-(1-Benzyl-piperidin-4-ylmethyl)-5,6-dimethoxy-indan-1-one

To a slurry of the title compound from Example 5 (1.82 gm, 6.3 mmol) in isopropylether (60 mL) was added benzylbromide (0.75 mL, 6.3 mmol) and triethanolamine (940 mg, 6.3 mmol). The slurry was stirred overnight, at 70°C, at which time high pressure liquid chromatography indicated that the starting material was mostly consumed. The reaction mixture was then filtered to remove precipitated triethanolamine hydrobromide. To the remaining solution was added ether saturated with hydrochloric acid (1.0 mL, 12 mmol), and the solvent was removed *in vacuo*. The residue was dissolved in 20 mL of hot isopropanol and allowed to cool to room temperature. The precipitated solid was filtered to provide 1.60 gm (61%) of the title compound as a white solid.

TLC (silica gel): R_f = 0.60 (90 : 10 methylene chloride/methanol); High Pressure Liquid Chromatography retention = 6.01 min (Zorbax C_8, 254 nm, 1 mL/min, eluted with 600:400:2:1 water/acetonitrile/triethylamine/acetic acid). ^1H NMR (of the free base, DMSO-d_6) δ 7.06 (s, 1H), 7.03 (s, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.41 (s, 2H), 3.19 (dd, 1H, J = 17.8, 8.2 Hz), 2.71-2.86 (m, 2H), 2.58-2.71 (m, 2H), 1.82-1.96 (m, 2H), 1.52-1.78 (m, 3H), 1.31-1.50 (m, 1H), 1.08-1.30 (m, 3H). FABMS $C_{24}H_{29}NO_3$ $(M + 1)^+ = 380$.

CLAIMS

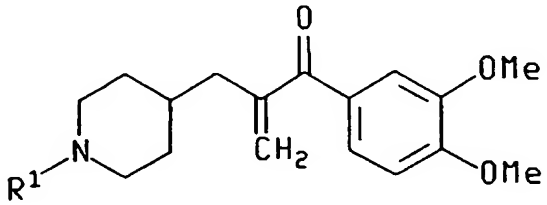
1. A compound of the formula



III

wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is (C_1-C_4)alkyl and R^3 is (C_1-C_4)alkyl or phenyl optionally substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo or trifluoromethyl.

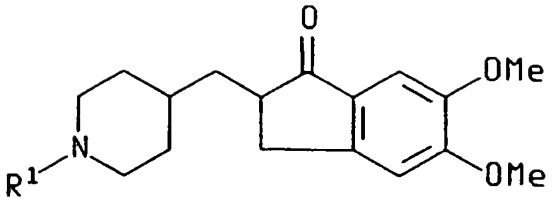
2. A compound of the formula



II

wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is (C_1-C_4)alkyl and R^3 is (C_1-C_4)alkyl or phenyl optionally substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo or trifluoromethyl.

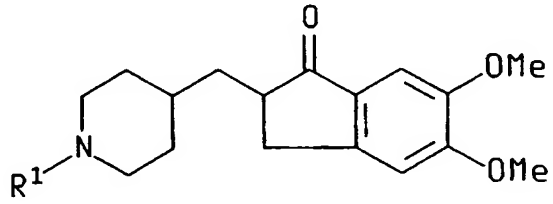
3. A compound of the formula



I

wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is (C_1-C_4)alkyl and R^3 is (C_1-C_4)alkyl or phenyl optionally substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo or trifluoromethyl.

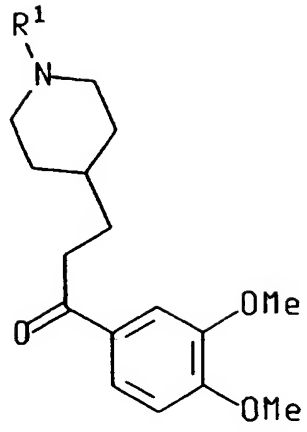
4. A process for preparing a compound of the formula



I

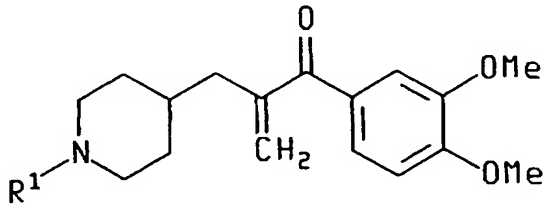
wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is (C_1-C_4)alkyl and R^3 is (C_1-C_4)alkyl or phenyl optionally substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo or trifluoromethyl, comprising

a) reacting a compound of the formula



III

wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is (C_1-C_4)alkyl and R^3 is (C_1-C_4)alkyl or phenyl optionally substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo or trifluoromethyl, with a methenylation agent to form a compound of the formula



II

wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is (C_1-C_4)alkyl and R^3 is (C_1-C_4)alkyl or phenyl optionally substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo or trifluoromethyl and;

b) reacting said compound of formula II, so formed, with a strong acid.

5. A process according to claim 4 wherein said methenylation agent is tetramethyldiaminomethane in acetic anhydride.

6. A process according to claim 5 wherein said tetramethyldiaminomethane and acetic anhydride are added in excess.

7. A process according to claim 6 wherein said tetramethyldiaminomethane

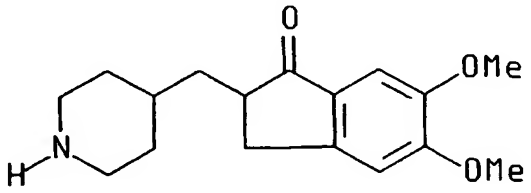
comprises 2 equivalents and said acetic anhydride comprises 4 equivalents.

8. A process according to claim 4 wherein said strong acid is sulfuric acid.

9. A process according to claim 8 wherein said sulfuric acid is concentrated sulfuric acid.

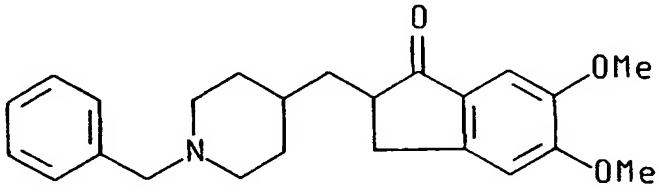
10. A process according to claim 9 wherein said concentrated sulfuric acid comprises 9 equivalents.

11. A process according to claim 4 further comprising the additional step of reacting the compound of formula I, wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is $(C_1$-$C_4)$alkyl and R^3 is $(C_1$-$C_4)$alkyl or phenyl optionally substituted with from one to three substituents independently selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo or trifluoromethyl, with hydroxide to form a compound of the formula



VI

and reacting said compound of formula VI so formed with a benzylhalide to form a compound of the formula



VII

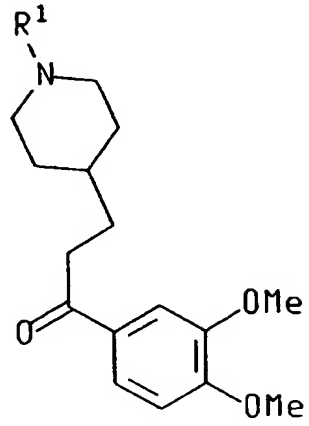
12. A process according to claim 11 wherein said benzyl halide is benzyl bromide.

13. A process according to claim 11 wherein said base is triethanolamine.

14. A process according to claim 11 wherein said compound of formula I is isolated by addition of the strongly acidic solution to ice/water followed by extraction with an organic solvent and removal of the organic solvent before the compound of

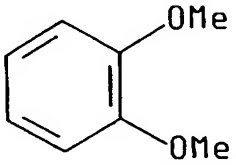
formula I is treated with a base.

15. A process for preparing a compound of the formula



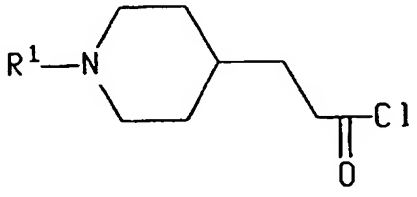
III

wherein R^1 is $R^2O(C=O)$- or $R^3(C=O)$-, R^2 is (C_1-C_4)alkyl, and R^3 is (C_1-C_4)alkyl or phenyl optionally substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo or trifluoromethyl, comprising reacting a compound of the formula



IV

with a compound of the formula



V

wherein R^1 is as defined above, in the presence of a Lewis acid in a reaction inert solvent.

16. A process according to to claim 15 wherein said Lewis acid is aluminum trichloride and said reaction inert solvent is methylene chloride.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/IB 96/01076

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 29, no. 5, May 1986, pages 825-841, XP002018692 CRAGOE E.J. ET AL.: "Agents for the treatment of brain edema. 2. [(2,3,9,9a-Tetrahydro-3-oxo-9a-substituted -1H-fluoren-7-yl)oxy]alkanoic acids and some of their analogues" see scheme IV, page 827, compounds 8, 9, 10 and 11 ---	4-10,15, 16
X	EP,A,0 296 560 (EISAI CO., LTD.) 28 December 1988 see claims 1-8; examples 178,182 & US,A,4 895 841 (SUGIMOTO H. ET AL.) 23 January 1990 cited in the application ---	1,3
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
18 November 1996	17. 12. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Hartrampf, G

Form PCT/ISA/218 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/IB 96/01076

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 379 441 (RHONE-POULENC SANTÉ) 25 July 1990 see example 3	1,15,16

X	CHEMICAL & PHARMACEUTICAL BULLETIN, vol. 41, no. 3, March 1993, pages 529-538, XP002018693 ISHIHARA Y. ET AL.: "Central cholinergic agents. IV. Synthesis and acetylcholinesterase inhibitory activities of .omega.-[N-ethyl-N(phenylmethyl)amino]-1-phenyl-1-alkanones and their analogues with partial conformational restriction" see page 532, chart 6, compounds 25b and 26a	1,15,16
Y	see page 532, chart 6, compounds 26a, 27a and 10a	11-14

X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, no. 24, 24 November 1995, pages 4821-4829, XP002018694 SUGIMOTO H. ET AL.: "Synthesis and structure-activity relationships of acetylcholinesterase inhibitors: 1-Benzyl-4-[(5,6-dimethoxy-1-oxoindan-2-yl)methyl]piperidine hydrochloride and related compounds" see example 13A	3
Y	see scheme 2, page 4823, compounds 13a, 13b and 16	11-14

P,A	EP,A,0 711 756 (BAYER AG) 15 May 1996	1-16

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/IB 96/01076

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-296560	28-12-88	AT-T-	134618	15-03-96
		AU-B-	627151	20-08-92
		CN-A,B	1030752	01-02-89
		CN-A-	1073939	07-07-93
		DE-D-	3855028	04-04-96
		DE-T-	3855028	05-09-96
		EP-A-	0579263	19-01-94
		EP-A-	0673927	27-09-95
		EP-A-	0742207	13-11-96
		ES-T-	2083359	16-04-96
		FI-B-	95572	15-11-95
		FI-A-	952850	09-06-95
		FI-A-	962753	04-07-96
		JP-A-	1079151	24-03-89
		JP-A-	7252216	03-10-95
		NO-B-	177590	10-07-95
		RU-C-	2009128	15-03-94
		US-A-	4895841	23-01-90
		US-A-	5100901	31-03-92
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		AU-B-	622265	02-04-92
		AU-A-	4858490	26-07-90
		CA-A-	2008157	20-07-90
		JP-A-	2233675	17-09-90
		US-A-	5025013	18-06-91
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		CA-A-	2162081	09-05-96
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